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ORIGINAL ARTICLE

Glomerular and tubular dysfunctions and their relationship to adiponectin and oxidative stress in obese subjects

Eman Wagdy Gaber [a,*], **Hayam Abdel Meguid El Aggan** [b], **Hisham Salah El-Banawy** [c]

[a] *Department of Internal Medicine, Medical Research Institute, Alexandria University, Egypt*
[b] *Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt*
[c] *Department of Chemical Pathology, Medical Research Institute, Alexandria University, Egypt*

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KEYWORDS
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Summary *Background:* Obesity is an independent risk factor for renal disease. Microalbuminuria (MA) is the first sign of renal injury. Tubular dysfunction may present early in obesity but this has not been well studied. This study aimed at assessing glomerular and tubular dysfunctions and their relationship to adiponectin and oxidative stress in obese participants.
Methods: This study was conducted on 60 participants. Group 1 included 20 healthy individuals as controls, Group 2 included 20 obese individuals with normal albumin excretion rate (AER), and Group 3 included 20 obese individuals with increased AER. Clinical assessment, anthropometric measurements, and laboratory investigations included: estimation of serum high-density lipoprotein (HDL)-cholesterol, urinary albumin to creatinine ratio, and calculation of estimated glomerular filtration rate. Serum adiponectin, thiobarbituric acid-reactive substances (TBARs) as a marker of oxidative stress, and urinary gamma glutamyl transferase (UGGT) as a marker of tubular function were also estimated.
Results: The estimated glomerular filtration rate was higher in obese individuals with normal AER and significantly lower in those with abnormal AER compared to controls. Adiponectin was lower and TBARs and UGGT significantly higher in obese individuals with normal and abnormal AER than controls. Adiponectin was negatively correlated with TBARs, AER, and UGGT. There were positive correlations between TBARs and both AER and UGGT. HDL-cholesterol was positively correlated with adiponectin and negatively correlated with TBARs and UGGT.
Conclusion: Glomerular and tubular dysfunctions in obese individuals are related to low adiponectin and HDL-cholesterol levels and to oxidative stress. Tubular dysfunction precedes MA, so UGGT may be used as an early marker for obesity related nephropathy.

* Corresponding author. Medical Research Institute, Alexandria University, 10 Kamal el Deen Salah Street, Smoha, Alexandria, Egypt.
E-mail address: dr_emanwagdy@yahoo.com (E.W. Gaber).

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背景: 肥胖症是腎病的獨立危險因子，微白蛋白尿症(MA)則是腎損傷的最早期徵兆。腎小管功能障礙可能早於肥胖症初期出現，但這尚未獲得充分的研究探討。本研究旨在評估肥胖症患者間的腎小球與腎小管功能，並調查後兩者與adiponectin及氧化壓力的關係。
方法: 研究對象為60人，包括健康對照組的20人(組I)、20位白蛋白排泄率(AER)正常的肥胖症患者(組II)、及20位AER過高的肥胖症患者(組III)。所有人均接受了全面的體格與臨床評估、及醫學檢驗，後者包括：血清HDL-cholesterol、尿液albumin與creatinine比例、及腎絲球過濾率估算值(e-GFR)。此外，氧化壓力指標包括血清adiponectin、thiobarbituric acid-reactive substances (TBARs)；腎小管功能指標則為尿液的gamma glutamyl transferase (UGGT)濃度。
結果: 相比於對照組，較高的e-GFR出現在AER正常的肥胖症患者間；明顯較低的e-GFR則出現在AER異常的肥胖症患者之中。同時，不論AER是否正常，肥胖症患者的adiponectin濃度較低，TBARs與UGGT則明顯較高。Adiponectin與TBARs、AER、及UGGT三者之間存在負相關的關係；TBARs則與AER及UGGT兩者呈正相關。此外，HDL-cholesterol與adiponectin呈正相關，與TBARs及UGGT兩者則呈負相關的關係。
結論: 肥胖症患者的腎小球與腎小管功能障礙與較低的adiponectin及HDL-cholesterol有關，亦與氧化壓力有關。腎小管功能障礙在MA之前出現，因此UGGT可以作為肥胖症相關腎病變的早期指標。

Introduction

The incidence and prevalence of obesity have increased over the past 2 decades and become a worldwide public health problem. Several epidemiologic studies have clearly demonstrated that obesity is an independent risk factor for the onset, aggravated course, and poor outcomes of chronic kidney disease (CKD).[1] Obesity is associated with various functional and structural lesions of the kidney. The spectrum ranges from glomerulomegaly with or without focal segmental glomerulosclerosis, to diabetic nephropathy, to carcinoma of the kidney and nephrolithiasis.[2]

Obesity is associated with worsening albuminuria, proteinuria, and end-stage renal disease (ESRD). Therefore, early screening of CKD for obese individuals may lead to more successful intervention and management of CKD, and is beneficial to prevent further renal damage. Microalbuminuria (MA) is the current first sign of renal injury, as well as the predictor of progression to ESRD.[3]

Adiponectin is a 30-kDa plasma protein primarily secreted by adipocytes. Plasma adiponectin levels are reduced with increasing visceral obesity and tightly correlate with insulin resistance and development of Type 2 diabetes.[4] Adiponectin has been shown to support normal podocyte function.[5] Weight gain-induced decline in adiponectin may disrupt podocyte function leading to albuminuria.[6]

Oxidative stress plays an important role in the pathogenesis and progression of many renal diseases.[7] It has been reported that, obesity is not only associated with increased oxidant stress but also with reduced antioxidant defense mechanisms, including decreased erythrocyte glutathione and glutathione peroxidase.[8] Podocytes are known to be particularly susceptible to oxidative injury and reactive oxygen species (ROS) play a critical role in podocyte injury and glomerular dysfunction.[9]

Increased oxidative stress in obesity contributes to adipokine dysregulation, inflammation, and insulin resistance.[10] Oxidative stress has been linked with adiponectin deficiency.[11] Evidence indicates that thiobarbituric acid reactive substances (TBARs) can be used as a reliable index of oxidative stress in man because they reflect lipid peroxidation.[12]

Many previous studies on obesity related nephropathy have focused on functional and structural changes in the glomeruli and a little is known about the presence of tubular dysfunction. Obese individuals with minimal apparent nephropathy, as evidenced by MA, have significant alteration in tubular functions .[13]

Tubular damage as suggested by enzymuria and tubular proteinuria is a recognized feature of glomerulonephritis with clinical albuminuria and diabetic nephropathy.[14] Moreover, it has been recognized that changes within tubulointerstitium are more important than glomerulopathy in terms of renal prognosis in patients with CKD.[15]

Gamma glutamyl transferase (GGT) is an enzyme located in the brush border of the proximal convoluted tubules of the kidney. Urinary GGT level has been reported to increase during renal tubular damage and can be used as a marker of tubular function.[16] Tubular dysfunction may present early in obesity but this has not been well studied. This study aimed at assessing glomerular and tubular dysfunctions and their relationship to adiponectin and oxidative stress in obese individuals.

Participants and methods

After approval of the Ethical Committee of the Medical Research Institute, the present study was conducted on 60 unknown individuals directly recruited from the outpatient clinic of the Internal Medicine Department of the Medical Research Institute, Alexandria, Egypt. Written informed consents were taken from all participants and they were divided into three groups:

- Group 1 included: 20 apparently healthy volunteers (10 females and 10 males) with body mass index (BMI) <25 kg/m^2.
- Group 2 included: 20 obese individuals (10 females and 10 males) with BMI $>$ 30 kg/m^2 and normal albumin excretion rate (AER).
- Group 3 included: 20 obese individuals (12 females and 8 males) with BMI $>$ 30 kg/m^2 and increased AER.

All individuals involved in this study were free from diabetes, chronic liver disease, connective tissue disease, cardiac diseases, respiratory diseases, infections, and malignancy.

To all studied participants the followings were done:

1. Detailed history taking and thorough clinical examination with special stress on clinical manifestations of renal disease.
2. Anthropometric measurements included: triceps skin fold, mid-arm circumference, mid-arm muscle circumference, waist circumference (WC) and calculation of BMI.[17]
3. Twelve-lead electrocardiogram.
4. Ultrasonography of kidneys
5. Laboratory investigations included: estimation of serum levels of fasting and two hours postprandial glucose (FSG, PPG),[18] serum uric acid,[18] cholesterol [total, high- and low-density lipoprotein-cholesterol (HDL-C, LDL-C)], and triglycerides (TG)[18]; estimation of serum activities of alanine aminotransferase, aspartate aminotransaminase, and GGT.[18] Renal function tests included: complete urine analysis, estimation of serum urea and creatinine, and calculation of estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation[18]; estimation of urinary albumin to creatinine ratio (ACR) to assess AER[19]; estimation of urinary GGT enzyme (UGGT) by enzyme linked immunosorbant assay (ELISA) technique as a marker of renal tubular damage.[20] All these analyses were conducted on the Olympus AU400 clinical chemistry analyzer (Olympus, Tokyo, Japan). Estimation of serum thiobarbituric acid (TBA)-reactive substances (TBARs), as a marker of the oxidative stress,[21] the TBARs assay measures the amount of malondialdehyde and malondialdehyde-like substances formed by the lipid peroxidation process. Deproteinization of the EDTA plasma by trichloroacetic acid was done and malondialdehyde in the protein free supernatant was allowed to react with TBA in acidic media in a boiling water bath to form a rosy colored product that is measured spectrophotometrically against TBA reagent blank at 532 nm and compared with a standard solution similarly treated. Estimation of serum adiponectin level: using a noncompetitive sandwich ELISA (Cat#: ELH-ADIPONECTIN-001; RayBiotech, Inc., Norcross, GA, USA).[22]

The serum samples, standards, and controls were pipetted into microplate wells coated with antihuman adiponectin antibodies. After incubation and washing steps, biotinylated antihuman adiponectin antibodies were added. After the second incubation and washing steps, horseradish peroxidase-conjugated streptavidin was added. After the third incubation and washing steps, a tetramethylbenzidine substrate solution was added followed, after incubation, by adding a stopping solution. The yellow color developed was proportional to the amount of adiponectin bound. The intensity of this color was measured at 450 nm and the concentration of adiponectin was obtained from a standard curve.

Statistical analysis

Data were analysed using SPSS software. Results are expressed as means and standard deviations (SD). Abnormally distributed data were analysed by Mann-Whitney test. Statistical comparisons between two percentages were made by using the Chi-square test. Statistical comparisons of three groups were made using one-way ANOVA test with *posthoc* comparisons. The correlations between different variables were evaluated by Pearson or Spearman correlation coefficients according to the distribution of variable (continuous or discontinuous quantitative variables respectively). Statistical significance was assessed at $p < 0.05$. All calculated p-values were two-tailed.

Multiple regression analyses were carried out to investigate the relationship between dependent variables (BMI, adiponectin, TBARs, and UGGT) and several other anticipated independent predictor variables (WC, blood pressure, eGFR, ACR, lipid profile, uric acid, and FSG). The backward stepwise method was used to choose only the most significant predictors of them to be included into the final multiple regression models. The nonsignificant predictor variables were sequentially removed one by one.

Results

The clinical and laboratory data are presented in Tables 1—10. The mean systolic blood pressure, FSG, PPG, total cholesterol, LDL-C, TG, and uric acid were significantly higher in obese individuals than controls. The mean HDL-C was significantly lower in obese individuals than controls (42.45 ± 5.4 and 43.00 ± 8.44 vs. 50.85 ± 9.57 mg/dL, $p = 0.002$). There were significant positive correlations between BMI and both WC and blood pressure and between BMI and ACR in obese individuals with abnormal AER. The eGFR was higher in obese individuals with normal AER compared to controls and was significantly lower in obese individuals with abnormal AER compared to obese individuals with normal AER and controls (87.62 ± 8.22 vs. 99.23 ± 13.54 and 96.67 ± 7.22 mL/min, $p = 0.001$).

The mean serum adiponectin level was lower in obese individuals than controls, but this lower adiponectin level was statistically significant only in obese individuals with abnormal AER compared to controls (4.04 ± 2.1 vs. 6.04 ± 3.39 μg/ml, $p = 0.049$). The median serum adiponectin levels were nonsignificantly higher in females of each of the three studied groups than males. The mean TBARs level was significantly higher in obese individuals with normal and abnormal AER compared to controls (15.45 ± 3.99 and 15.65 ± 4.84 vs. 8.05 ± 1.54 μmol/l, $p < 0.0001$). The mean UGGT level was significantly higher in obese individuals with normal and abnormal AER than controls (61.3 ± 25.87 and 77.6 ± 33.51 vs. 44.85 ± 14.06 IU/l, $p = 0.001$). Serum adiponectin level was negatively correlated with BMI, WC, systolic and diastolic blood pressure, TBARs, and UGGT and positively correlated with HDL-C. There was a significant negative correlation between serum adiponectin and ACR in obese individuals with abnormal AER. There were significant positive correlations between serum TBARs and each of BMI, WC, systolic and diastolic blood pressure, and UGGT and a significant negative correlation between serum TBARs and HDL-C. Also, there was a significant positive correlation between TBARs and ACR in obese individuals with abnormal

Table 1 Some clinical data of all studied obese and control participants.

Parameter	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	*p*	G1/G2	GI/G3	G2/3
Age (y)	38.90 ± 7.03	38.95 ± 6.72	42.70 ± 6.33	0.130	NS	NS	NS
SBP (mmHg)	116.0 ± 9.95	130.50 ± 13.17	133.0 ± 13.02	<0.001	Sig	Sig	NS
DBP (mmHg)	76.0 ± 5.03	80.0 ± 8.58	81.0 ± 10.71	0.149	NS	NS	NS
BMI (kg/m^2)	23.25 ± 1.42	37.87 ± 6.31	39.64 ± 3.17	<0.0001	Sig	Sig	NS
TSF (cm)	0.72 ± 0.09	2.91 ± 0.49	3.04 ± 0.31	<0.0001	Sig	Sig	NS
MAC (cm)	32.10 ± 3.46	45.30 ± 7.55	48.55 ± 4.90	<0.0001	Sig	Sig	NS
MAMC (cm)	29.37 ± 3.46	35.79 ± 6.25	38.97 ± 4.22	<0.0001	Sig	Sig	Sig
WC (cm)	83.15 ± 2.83	123.35 ± 12.73	122.55 ± 8.64	<0.0001	Sig	Sig	NS

BMI = body mass index; DBP = diastolic blood pressure; MAC = mid arm circumference; MAMC = mid arm muscle circumference; SBP = systolic blood pressure; SD = standard deviation; TSF = triceps skin fold; WC = waist circumference.

AER. The UGGT was positively correlated with BMI, WC and ACR and negatively correlated with HDL-C.

The final multiple regression analyses with BMI (an indicator of obesity) as the dependent variable revealed that, in all studied participants, systolic blood pressure, uric acid and TBARS were significant positive predictors of obesity. In obese individuals with normal AER (Group 2), TBARS were significant positive predictors of obesity and in obese individuals with increased AER (Group 3); adiponectin was a significant negative predictor of obesity. On using adiponectin as a dependent variable, in all studied participants TBARs were negative predictors. In Group 2, WC, ACR, and cholesterol were negative predictors, and in Group 3, TBARs, ACR, and LDL-C were negative predictors, while HDL-C was a positive predictor. On using TBARs as a dependent variable, in all studied participants adiponectin and HDL-C were negative predictors, while BMI, systolic blood pressure and UGGT were positive predictors. In Group 2, HDL-C was a negative predictor, while BMI, systolic blood pressure, LDL-C, triglycerides, ACR, and UGGT were positive predictors. In Group 3 adiponectin and eGFR were negative predictors, while BMI, systolic blood pressure, FSG, cholesterol, triglycerides, and UGGT were positive predictors. On using UGGT as a dependent variable, in all studied participants WC and TBARs were positive predictors. In Group 2 WC, ACR, cholesterol, and TBARs were positive predictors and in Group 3 LDL-C, ACR, and TBARs were positive predictors.

Discussion

Obesity represents an underestimated risk factor for renal disease. Obese patients are three times more likely to develop renal disease than nonobese patients.[23] In this work, obese individuals had a significant association between increased overall obesity as measured by BMI and increased visceral fat as measured by WC. In addition, they have higher levels of systolic blood pressure, FSG, PPG, total cholesterol, LDL-C, TG, and uric acid and lower level of HDL-C than controls. On using final multiple regression analysis in all the studied participants, systolic blood pressure and uric acid were significant positive predictors of obesity. These findings indicate that obesity is accompanied by one or more of the components of metabolic syndrome, which is strongly associated with the development of renal disease.[24] These results are consistent with the results of many other studies.[25–27]

Table 2 Fasting and post prandial serum glucose and lipid profile of all studied obese and control participants.

Parameter	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	*p*	G1/G2	G1/G3	G2/3
FSG (mg/dL) Mean ± SD	88.80 ± 8.07	95.45 ± 8.20	98.40 ± 7.96	0.001	Sig	Sig	NS
PPSG (mg/dL) Mean ± SD	106.35 ± 4.75	112.35 ± 10.19	114.20 ± 11.40	0.025	Sig	Sig	NS
TC (mg/dL) Mean ± SD	164.20 ± 2.23	204.65 ± 29.45	208.20 ± 35.67	<0.0001	Sig	Sig	NS
HDL-C (mg/dL) Mean ± SD	50.85 ± 9.57	42.45 ± 5.40	43.00 ± 8.44	0.002	Sig	Sig	NS
LDL-C (mg/dL) Mean ± SD	96.70 ± 20.65	139.60 ± 28.82	132.25 ± 32.21	<0.0001	Sig	Sig	NS
TG (mg/dL) Mean ± SD	93.55 ± 32.37	119.90 ± 35.24	129.20 ± 38.47	0.007	Sig	Sig	NS

FSG = fasting serum glucose; HDL-C = High density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol; PPG = post prandial glucose; TC = total cholesterol.

Table 3 Serum urea, creatinine, estimated glomerular filtration rate and serum uric acid of all studied participants.

Parameter	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	*p*	G1/G2	G1/G3	G2/3
Urea (mg/dL)							
Mean ± SD	24.35 ± 4.18	25.40 ± 4.19	28.75 ± 8.37	0.056	NS	NS	NS
Cr (mg/dL)							
Mean ± SD	0.81 ± 0.10	0.85 ± 0.12	0.84 ± 0.10	0.449	NS	NS	NS
eGFR (mL/min)							
Mean ± SD	96.67 ± 7.22	99.23 ± 13.54	87.62 ± 8.22	0.001	NS	Sig	Sig
UA (mg/dl)							
Mean ± SD	4.74 ± 0.58	5.45 ± 0.73	5.97 ± 0.48	<0.0001	Sig	Sig	Sig

Cr = serum creatinine; eGFR = estimated glomerular filtration rate; UA = uric acid.

Obesity is characterized by dysregulated production of adipocytokines (leptin, tumor necrosis factor-α, adiponectin, free fatty acids, and resistin) that play important roles in the pathogenesis of insulin resistance and associated metabolic complications such as impaired glucose tolerance, dyslipidemia, and hypertension.[28]

Our study demonstrated that, eGFR was higher in obese individuals with normal AER and was significantly lower in those with increased AER. A similar association between albuminuria and GFR has been reported in other studies.[29–31] Previous experimental and clinical studies of obesity confirmed the presence of early hemodynamic changes, which are characterized by an increase GFR and accompanied by variable increments in albumin excretion.[30,31] Then, once macroalbuminuria sets in, GFR begins to decline.

The first sign of renal damage in obesity is MA, which indicates the potential risk of the progression to renal insufficiency.[3] In the current study there was a significant positive correlation between BMI and ACR in obese individuals with abnormal AER. Other studies have supported this association.[32,33] The mechanism of obesity-associated proteinuria is unclear but may include hyperfiltration, increased renal venous pressure, glomerular hypertrophy, hyperlipidemia, and increased synthesis of vasoactive and fibrogenic substances, including angiotensin II, insulin, leptin, and transforming growth factor-β1.[34]

In this work, although plasma adiponectin levels were higher in females than males, yet these levels did not reach the level of significance due to the small sample size. The higher adiponectin levels in females have been reported in other studies.[35] This can be explained by the well-known difference between males and females in fat distribution and metabolism,[36] and the selective inhibition of the secretion of high molecular weight adiponectin by testosterone.[37]

In the present study, the mean adiponectin level was lower in obese individuals than controls and was negatively correlated with BMI and WC. In addition, the final multiple regression analysis revealed that adiponectin was a significant negative predictor of obesity (BMI) in obese individuals with increased AER, and WC was a negative predictor of adiponectin in obese individuals with normal AER. Adiponectin reduction in obesity has been documented in many other studies.[38,39] Reduced adiponectin level in obesity can be explained by the presence of the chronic inflammatory state in obesity with increased production of proinflammatory cytokines such as tumor necrosis factor-α, and interleukins-6 and -18 that reduce adiponectin gene expression with subsequent decreased adiponectin secretion.[40] In addition, increased fat mass results in a hypoxic microenvironment and suppression of adiponectin gene expression via the hypoxia-induced factor-1.[41]

Table 4 Urinary albumin/creatinine ratio and gamma glutamyl transferase and serum thiobarbituric acid reactive substances and adiponectin of all studied participants.

Parameter	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)	*p*	G1/G2	G1/G3	G2/3
ACR (mg/g)							
Mean ± SD	28.24 ± 1.12	27.10 ± 1.32	191.70 ± 60.57	<0.0001	NS	Sig	Sig
UGGT (IU/L)							
Mean ± SD	44.85 ± 14.06	61.30 ± 25.87	77.60 ± 33.51	0.001	Sig	Sig	NS
TBARS (μM)							
Mean ± SD	8.05 ± 1.54	15.45 ± 3.99	15.65 ± 4.84	<0.0001	Sig	Sig	NS
Adiponectin (μg/mL)							
Mean ± SD	6.04 ± 3.39	4.39 ± 2.38	4.04 ± 2.10	0.049	NS	Sig	NS

ACR = urinary albumin/creatinine ratio; TBARS = serum thiobarbituric acid reactive substances; UGGT = urinary gamma glutamyl transferase.

Table 5 Adiponectin levels in males and females of the three studied groups.

Group 3		Group 2		Group 1		
Female ($n = 16$)	Male ($n = 4$)	Female ($n = 10$)	Male ($n = 10$)	Female ($n = 10$)	Male ($n = 10$)	Adiponectin (μg/mL)
1.32—7.07	2.23—8.74	2 .09—5.58	1.59—10.77	1.93—12.76	2.67—12.88	Range
4.51	3.58	4.72	2.89	5.65	4.73	Median
0.705		0.364		0.597		*P*

P value for Mann—Whitney *p* value between males and females in each group

Oxidative stress (OS) plays an important role in a variety of renal diseases including glomerulonephritis and can contribute to albuminuria.[7,9] In the present study, TBARs were significantly higher in obese individuals than controls. In addition, the final multiple regression analysis confirmed that TBARs and BMI were significant positive predictors of each other in all participants and in both obese groups with normal and increased AER. These data are in agreement with other previously published data.[42,43] Obesity has been described as a state of chronic OS. There are several possible contributors to OS in obesity, including hyperglycemia, increased muscle activity to carry excessive weight, elevated tissue lipid levels, inadequate antioxidant defenses, chronic inflammation, and hyperleptinemia.[44]

In the present study, the final multiple regression analysis showed that triglycerides, total cholesterol, and LDL-C were positive predictors of TBARs. In addition, this study demonstrated a significant inverse correlation between TBARs and both adiponectin and HDL-C, and a significant positive correlation between adiponectin and HDL-C. These results were also proved by the final multiple regression analysis when using TBARs or adiponectin as a dependent variable. Similar results have been shown in other studies.[45,46] The present results indicate that the increased OS in obese individuals can be explained by the decreased adiponectin level that may lead to deficiency of the protective HDL-C. As it was found that there is a strong inverse association between adiponectin and fractional catabolic rate of ApoA-1 which is a major structural apolipoprotein of HDL-C.[47] Deficiency of HDL-C in obese individuals was associated with elevated levels of oxidative stress and impairment of its antioxidant effects.[48]

In this work, albuminuria was positively correlated with TBARs and negatively correlated with adiponectin. These results were also confirmed on using the final multiple regression analysis which showed that ACR was a positive predictor of TBARs in the obese group with normal AER, and was a negative predictor of adiponectin in both obese groups with normal and increased AER. Similarly, an inverse association between adiponectin and albuminuria has been previously demonstrated in other studies.[49,50] A previous experimental study has demonstrated that adiponectin deficient mice exhibited increased albuminuria and fusion of podocyte foot processes, which indicates that adiponectin deficiency contributes to altered permeability, probably via podocyte dysfunction.[5] One potential pathway by which adiponectin may provide protection against albuminuria and podocyte permeability is via reduction of OS.[5,51,52]

In the current study, albuminuria was associated with systolic and diastolic blood pressure. A similar association has been reported in other studies.[53,54] Increased intraglomerular pressure is considered a major factor for

Table 6 Some statistically significant correlations in all studied obese participants.

Parameters	r	*p*
Serum adiponectin with:		
Systolic blood pressure	−0.379	0.016
Diastolic blood pressure	−0.391	0.013
Body mass index	−0.487	0.001
Waist circumference	−0.524	0.001
High density lipoprotein cholesterol	0.472	0.002
Urinary gamma glutamyl transferase	−0.542	<0.001
Serum thiobarbituric acid reactive substances	−0.624	<0.001
Serum thiobarbituric acid reactive substances with:		
Systolic blood pressure	0.636	<0.001
Diastolic blood pressure	0.610	<0.001
Body mass index	0.615	<0.001
Waist circumference	0.514	0.001
High density lipoprotein cholesterol	−0.529	<0.001
Urinary gamma glutamyl transferase	0.524	0.001
Urinary gamma glutamyl transferase with:		
Body mass index	0.558	<0.001
Waist circumference	0.474	0.002
High density lipoprotein cholesterol	−0.385	0.014
Urinary albumin/creatinine ratio	0.354	0.025
Body mass index with:		
Waist circumference	0.659	<0.001
Systolic blood pressure	0.455	0.003
Diastolic blood pressure	0.362	0.022

Table 7 Some statistically significant correlations in the studied obese participants with abnormal albumin excretion rate.

Parameters	r	*p*
Urinary albumin/creatinine ratio with:		
Systolic blood pressure	0.668	0.001
Diastolic blood pressure	0.637	0.003
Body mass index	0.605	0.005
Adiponectin	−0.749	<0.001
Serum thiobarbituric acid reactive substances	0.685	<0.001

Table 8 The final multiple regression analyses in all studied participants ($n = 60$).

Significance	t	Beta	B	Significant predictors	Dependent variables
					1. BMI
0.040	2.104		17.702	Constant	$r = 0.878$, $r^2 = 0.77$, adjusted $r^2 = 0.749$,
0.030	2.235	0.285	0.171	Systolic blood pressure	ANOVA shows $F = 36.19$, $p < 0.001$
0.045	2.057	0.161	1.742	Uric acid	
0.000	7.591	0.682	1.128	TBARs	
					2. Adiponectin
0.000	8.951		9.716	Constant	$r = 0.55$, $r^2 = 0.302$, adjusted $r^2 = 0.278$,
0.001	−3.602	−0.428	−0.233	TBARs	ANOVA shows Fv12.337, $p < 0.000$
					3. TBARs
0.655	−0.450		−1.791	Constant	$r = 0.9$, $r^2 = 0.81$, adjusted $r^2 = 0.789$,
0.000	4.331	0.413	0.250	BMI	ANOVA shows $F = 37.661$, $p < 0.000$
0.001	3.437	0.269	0.097	Systolic blood pressure	
0.017	2.454	0.192	0.034	UGGT	
0.024	−2.320	−0.168	−0.098	HDL-C	
0.054	−1.893	−0.131	−0.241	Adiponectin	
					4. UGGT
0.681	0.414		14.642	Constant	$r = 0.73$, $r^2 = 0.533$, adjusted $r^2 = 0.489$,
0.045	2.049	0.534	0.486	Waist circumference	ANOVA shows $F = 12.31$, $P<0.000$
0.004	2.990	0.450	2.522	TBARs	

B = regression coefficient; Beta = standardized coefficient; BMI = body mass index; HDL-C = high density lipoprotein cholesterol; TBARs = serum thiobarbituric acid reactive substances; UGGT = urinary gamma glutamyl transferase.

increased albumin excretion in hypertension. In addition, other factors such as decreased lysosomal activity with an upregulation of transforming growth factor-β1 resulting in increased albumin excretion in hypertension.[55]

The presence of increased proximal tubular enzymuria may be a surrogate marker of early renal injury to identify individuals who are at risk for renal disease with early intervention to prevent progression.[56] In the current

Table 9 The final multiple regression analyses in obese participants with normal albumin excretion rate ($n = 20$).

Significance	t	Beta	B	Significant predictors	Dependent variables
					1. BMI
0.154	1.520		18.867	Constant	$r = 0.941$, $r^2 = 0.885$, adjusted $r^2 = 0.818$,
0.000	5.616	1.182	1.866	TBARs	ANOVA shows $F = 36.193$, $p < 0.001$
					2. Adiponectin
0.001	4.195		56.824	Constant	$r = 0.944$, $r^2 = 0.891$, adjusted $r^2 = 0.828$
0.000	−5.201	−0.998	−0.187	Waist circumference	ANOVA shows $F = 14.07$, $p < 0.0001$
0.003	−3.961	−0.953	−1.714	ACR	
0.003	−3.724	−0.615	−0.050	Cholesterol	
					3. TBARs
0.569	0.594		3.763	Constant	$r = 0.998$, $r^2 = 0.996$, adjusted $r^2 = 0.991$,
0.000	11.103	0.541	0.343	BMI	ANOVA shows $F = 182.6$, $p < 0.0001$
0.001	5.305	0.186	0.056	Systolic blood pressure	
0.001	−5.586	−0.314	−0.232	HDL-C	
0.000	12.482	0.428	0.059	LDL-C	
0.001	5.576	0.252	0.029	Triglycerides	
0.039	2.466	0.145	0.436	ACR	
0.001	5.132	0.239	0.037	UGGT	
					4. UGGT
0.009	−3.268		−388.97	Constant	$r = 0.985$, $r^2 = 0.971$, adjusted $r^2 = 0.939$,
0.001	4.53	0.76	1.545	Waist circumference	ANOVA shows $F = 30.04$, $p < 0.0001$
0.01	3.247	1.44	1.265	Cholesterol	
0.06	2.062	0.36	7.033	ACR	
0.001	5.032	1.338	8.671	TBARs	

ACR = urinary albumin/creatinine ratio; B = regression coefficient; Beta = standardized coefficient; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TBARs = Serum thiobarbituric acid reactive substances; UGGT = Urinary gamma glutamyl transferase.

Table 10 The final multiple regression analyses in obese participants with increased albumin excretion rate ($n = 20$).

Significance	t	Beta	B	Significant predictors	Dependent variables
					1. BMI
0.000	32.026		42.985	Constant	$r = 0.551$, $r^2 = 0.303$, adjusted $r^2 = 0.265$,
0.012	−2.799	−0.551	−0.83	Adiponectin	ANOVA shows $F = 7.837$, $p < 0.012$
					2. Adiponectin
0.585	−0.572		−4.108	Constant	$r = 0.978$, $r^2 = 0.956$, adjusted $r^2 = 0.88$
0.008	3.633	0.554	0.138	HDL-C	ANOVA shows $F = 12.606$, $p < 0.001$
0.048	−2.426	−1.485	−0.097	LDL-C	
0.002	−4.722	−1.699	−0.059	ACR	
0.028	−2.755	−0.703	−0.306	TBARs	
					3. TBARs
0.292	−1.14		−22.042	Constant	$r = 0.984$, $r^2 = 0.967$, adjusted $r^2 = 0.911$,
0.05	2.36	0.445	0.679	BMI	ANOVA shows $F = 17.247$, $p < 0.0001$
0.001	5.724	1.139	0.423	Systolic blood pressure	
0.003	4.488	0.779	0.473	FSG	
0.005	4.036	1.554	0.211	Cholesterol	
0.05	2.37	0.383	0.048	Triglycerides	
0.012	−3.371	−0.796	−0.468	eGFR	
0.034	−2.629	−0.354	−0.813	Adiponectin	
0.012	3.354	0.434	0.063	UGGT	
					4. UGGT
0.683	0.42		50.809	Constant	$r = 0.942$, $r^2 = 0.888$, adjusted $r^2 = 0.786$,
0.024	2.657	0.434	0.452	LDL-C	ANOVA shows $F = 8.766$, $p < 0.001$
0.001	4.357	1.201	0.665	ACR	
0.002	4.112	0.843	5.842	TBARs	

ACR = Urinary albumin/creatinine ratio; B = regression coefficient; Beta = standardized coefficient; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; FSG = fasting serum glucose; TBARs = serum thiobarbituric acid reactive substances; UGGT = urinary gamma glutamyl transferase.

study, obese patients with normal AER manifested renal tubular disorder evidenced by a significant increase in UGGT. Also, the final multiple regression analysis revealed that WC was a significant positive predictor of UGGT. In addition, obese patients with increased AER had concomitant renal tubular disorder evidenced by high UGGT and ACR was proved to be a significant positive predictor of UGGT in the final multiple regression analysis. In line with these results, increased UGGT has been reported in diabetic nephropathy.[57] The increased UGGT can be used as a simple, reliable, and noninvasive marker of early tubular involvement in the preclinical stage of obesity related nephropathy.

In the current study, TBARs were positively correlated with BMI, ACR and UGGT. These results suggest that obesity induced OS was accompanied by the occurrence of renal tubular damage and increased glomerular permeability as demonstrated by increased UGGT and albuminuria respectively. Similar association between OS, tubular enzymuria and increase in albuminuria has been reported with intravenous iron in patients with chronic kidney disease.[58]

The final multiple regression analysis confirmed that TBARs and UGGT were significant positive predictors of each other in all studied participants and in both obese groups with normal and increased AER. OS-induced tubular damage can be explained by the role of OS in the initiation and propagation of apoptosis in various cell types, as has been reported in other studies.[59] The proximal tubule is a major site of ROS production, due to its high transport activity supported by oxygen consuming metabolism, ROS and their products play an important role in apoptosis of proximal tubular cells (PTC).[60] Moreover, the presence of albuminuria and exposure of the PTC to an excess of albumin can induce renal proximal tubular cells apoptosis through generation of ROS.[61]

In addition, the final multiple regression analysis showed that eGFR was a negative predictor of TBARs in obese individuals with increased AER. Exposure of PTC to pathologically high concentrations of urinary proteins, including albumin, induces a number of potentially injurious biologic responses in tubular epithelial cells, including inflammation, apoptosis, production of ROS, and transition to a myofibroblast phenotype, ultimately contributing to tubulo-interstitial fibrosis and ESRD.[62]

Conclusion

Glomerular and tubular dysfunctions in obese individuals are related to low adiponectin and HDL-C levels and to oxidative stress. Tubular dysfunction precedes MA so UGGT may be used as an early marker for obesity related nephropathy.

References

1. Eknoyan G. Obesityand chronic kidney disease. *Nefrologia* 2011;**31**:397—403.

2. Hunley TE, Ma LJ, Kon V. Scope and mechanisms of obesity-related renal disease. *Curr Opin Nephrol Hypertens* 2010;**19**: 227—34.
3. Mathew AV, Okada S, Sharma K. Obesity related kidney disease. *Curr Diabetes Rev* 2011;**7**:41—9.
4. Kawano J, Arora R. The role of adiponectin in obesity, diabetes, and cardiovascular disease. *J Cardiometab Syndr* 2009;**4**:44—9.
5. Sharma K, Ramachandrarao S, Qiu G, Usui HK, McCue P, Chan L, et al. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest* 2008;**118**:1645—56.
6. Polak J, Kovacova Z, Jacek M, Klimcakova E, Kovacikova M, Sebela M, et al. An increase in plasma adiponectin multimeric complexes follows hypocaloric diet-induced weight loss in obese and overweight premenopausal women. *Clin Sci* 2007;**112**: 557—65.
7. Dobashi K, Ghosh B, Orak JK, Singh I, Singh AK. Kidney ischemia-reperfusion: modulation of antioxidant defenses. *Mol Cell Biochem* 2000;**205**:1—11.
8. Trevisan M, Browne R, Ram M, Muti P, Freudenheim J, Carosella AM, et al. Correlates of markers of oxidative status in the general population. *Am J Epidemiol* 2001;**54**:348—56.
9. Mayrhofer C, Krieger S, Huttary N, Chang MW, Grillari J, Allmaier G. Alterations in fatty acid utilization and an impaired antioxidant defense mechanism are early events in podocyte injury. A proteomic analysis. *Am J Pathol* 2009;**174**:1191—202.
10. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004;**114**: 1752—61.
11. Hattori Y, Akimoto K, Gross SS, Hattori S, Kasai K. Angiotensin-II-induced oxidative stress elicits hypoadiponectinaemia in rats. *Diabetologia* 2005;**48**:1066—74.
12. Gama CS, Salvador M, Andreazza AC, Lobato MI, Berk M, Kapczinski F, et al. Elevated serum thiobarbituric acid reactive substances in clinically symptomatic schizophrenic males. *Neurosci Lett* 2008;**433**:270—3.
13. Saliba J, Kasim NR, Tamboli RA, Isbell JM, Marks P, Feurer ID, et al. Roux-en-Y gastric bypass reverses renal glomerular but not tubular abnormalities in excessively obese diabetics. *Surgery* 2010;**147**:282—7.
14. Yaqoob M, McClelland P, Patrick AW, Stevenson A, Mason H, Bell GM. Tubular damage in microalbuminuric patients with primary glomerulonephritis and diabetic nephropathy. *Renal Fail* 1995;**17**:43—9.
15. Rodríguez-Iturbe B, García García G. The role of tubulointerstitial inflammation in the progression of chronic renal failure. *Nephron Clin Pract* 2010;**116**:c81—8.
16. Herget-Rosenthal S, Poppen D, Hüsing J, Marggraf G, Pietruck F, Jakob HG, et al. Prognostic value of tubular proteinuria and enzymuria in nonoliguric acute tubular necrosis. *Clin Chem* 2004;**50**:552—8.
17. Moreno LA, Rodríguez G, Guillén J, Rabanaque MJ, Leon JF, Ariño A. Anthropometric measurements in both sides of the body in the assessment of nutritional status in prepubertal children. *Eur J Clin Nutr* 2002;**12**:1208—15.
18. Burtis CA, Ashwod ER, Bruns DE. *Tietz textbook of clinical chemistry and molecular diagnostics*. 4th ed. Philadelphia: Elsevier Saunders Company; 2006. p. 868-72, 938-61, 803-7, 604-13, 797-8, 821-3, 808—12, respectively.
19. Powrie JK, Watts GF, Ingham JN. Role of glycaemic control in development of microalbuminuria in patients with insulin dependent diabetes. *BMJ* 1994;**309**:1608—12.
20. Adams R, McClure JJ, Gossett KA, Koonce KL, Ezigbo C. Evaluation of a technique for measurement of gamma-glutamyltranspeptidase in equine urine. *Am J Vet Res* 1985;**46**:147—50.
21. Bernhiem F, Bernhiem ML, Wilbur KM. The reaction between thiobarbituric acid and oxidative products of certain lipids. *J Biol Chem* 1984;**174**:257—8.
22. Iglseder B, Mackevics V, Stadlmayer A, Tasch G, Ladurner G, Paulweber B. Plasma adiponectin levels and sonographic phenotypes of subclinical carotid artery atherosclerosis. *Stroke* 2005;**36**:2577—82.
23. Ejerblad E, Fored M, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk of chronic renal failure. *J Am Soc Nephrol* 2006;**17**:1695—702.
24. Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. *J Am Soc Nephrol* 2006;**17**(Suppl. 2): S81—5.
25. Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr* 2002;**76**: 743—9.
26. Scaglione R, Di Chiara T, Cariello T, Licata G. Visceral obesity and metabolic syndrome: two faces of the same medal? *Inter Emerg Med* 2010;**5**:111—9.
27. Adamu GB, Geoffrey CO, Bala GS, Ibrahim SA, Sani SH, Tambaya MA. Relationship between random blood sugar and body mass index in an African population. *Int J Diabetes Metabol* 2006;**14**:144—5.
28. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *Endocrinol Metab* 2008;**93**:S64—73.
29. Pinto-Sietsama SJ, Janssen WMT, Hillege HL, Navis G, De Zeeuw D, De Jong PE. Urinary albumin excretion is associated with renal functional abnormalities in a non-diabetic population. *J Am Soc Nephrol* 2000;**11**:1882—8.
30. Henegan JR, Bigler SA, Henegan LK. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* 2001;**12**:1211—7.
31. Rea DJ, Heinbach JK, Grande JP, Textor SC, Taler SJ, Prieto M, et al. Glomerular volume and renal histology in obese and non-obese living kidney donors. *Kidney Int* 2006;**70**:1636—41.
32. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006;**144**:21—8.
33. Ferris M, Hogan SL, Chin H, Shoham DA, Gipson DS, Gibson K, et al. Obesity, albuminuria, and urinalysis findings in US young adults from the Add Health Wave III Study. *Clin J Am Soc Nephrol* 2007;**2**:1207—14.
34. Rutkowski P, Klassen A, Sebekova K, Bahner U, Heidland A. Renal disease in obesity: the need for greater attention. *J Ren Nutr* 2006;**16**:216—23.
35. Peake PW, Kriketos AD, Campbell LV, Shen Y, Charesworth JA. The metabolism of isoforms of human adiponectin: studies in human subjects and in experimental animals. *Eur J Endocrinol* 2005;**153**:409—17.
36. Blaak E. Gender differences in fat metabolism. *Curr Opin Clin Nutr Metab Care* 2001;**4**:499—502.
37. Xu A, Chan KW, Hoo RL, Wang Y, Tan KC, Zhang J, et al. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. *J Biol Chem* 2005;**280**:18073—80.
38. Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL, Murphy LJ. Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *Eur J Endocrinol* 2003;**149**:331—5.
39. Lihn AS, Bruun JM, He G, Pedersen SB, Jensen PF, Richelsen B. Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. *Mol Cell Endocrinol* 2004; **219**:9—15.
40. Nadler ST, Stoehr JP, Schueler KL, Tanimoto G, Yandell BS, Attie AD. The expression of adipogenic genes is decreased in obesity and diabetes mellitus. *Proc Natl Acad Sci U S A* 2000; **97**:11371—6.
41. Halberg N, Khan T, Trujillo ME, Asterholm IW, Attie AD, Sherwani S, et al. Hypoxia-inducible factor 1 induces fibrosis

and insulin resistance in white adipose tissue. *Mol Cel Biol* 2009;**16**:4467—83.
42. Ozata M, Mergen M, Oktenli C, Aydin A, Sanisoglu SY, Bolu E, et al. Increased oxidative stress and hypozincemia in male obesity. *Clin Biochem* 2002;**35**:627—31.
43. Keaney JF, Larson MG, Vasan RS, Perticone F, Ceravolo R, Candigliota M, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arterioscler Thromb Vasc Biol* 2003;**23**:434—9.
44. Vincent HK, Taylor AG. Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans. *Int J Obes* 2006; **30**:400—18.
45. Barazzoni R, Bernardi A, Biasia F, Semolic A, Bosutti A, Mucci M, et al. Low fat adiponectin expression is associated with oxidative stress in nondiabetic humans with chronic kidney disease—impact on plasma adiponectin concentration. *Am J Physiol Regul Integr Comp Physiol* 2007;**293**: R47—54.
46. Hansel B, Giral P, Norbcourt E, Chantepie S, Bruckert E, Chapman MJ, et al. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. *J Clin Endocrinol Metabol* 2004;**89**: 4963—71.
47. Marini MA, Succurro E, Frontoni S, Hribal ML, Andreozzi F, Lauro R, et al. Metabolically healthy but obese women have an intermediate cardiovascular risk profile between healthy nonobese women and obese insulin-resistant women. *Diabetes Care* 2007;**30**:2145—7.
48. Van Lenten BJ, Navab M, Shih D, Fogelman AM, Lusis AJ. The role of high-density lipoproteins in oxidation and inflammation. *Trends Cardiovasc Med* 2001;**11**:155—61.
49. Yano Y, Hoshide S, Ishikawa J, Hashimoto T, Eguchi K, Shimada K. Differential impacts of adiponectin on low-grade albuminuria between obese and nonobese persons without diabetes. *J Clin Hypertens (Greenwich)* 2007;**9**:775—82.
50. Jorsal A, Tarnow L, Frystyk J, Lajer M, Flyvbjerg A, Parving HH, et al. Serum adiponectin predicts all-cause mortality and end stage renal disease in patients with type I diabetes and diabetic nephropathy. *Kidney Int* 2008;**74**:649—54.
51. Ouedraogo R, Wu X, Xu S, Fuchsel L, Motoshima H, Mahadev K, et al. Adiponectin suppression of high-glucose-induced reactive oxygen species in vascular endothelial cells: evidence for involvement of a cAMP signaling pathway. *Diabetes* 2006;**55**: 1840—6.
52. Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, et al. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. *Circulation* 2007;**115**:1408—16.
53. Hoffmann IS, Jimenez E, Cubeddu LX. Urinary albumin excretion in lean, overweight and obese glucose tolerant individuals: its relationship with dyslipidaemia, hyperinsulinaemia and blood pressure. *J Hum Hypertens* 2001;**15**:407—12.
54. Forman JP, Fisher NDL, Schopick EL, Curhan GC. Higher levels of albuminuria within the normal range predict incident hypertension. *J Am Soc Nephrol* 2008;**19**:1983—8.
55. Russo LM, Osicka TM, Bonnet F, Jerums G, Comper WD. Albuminuria in hypertension is linked to altered lysosomal activity and TGF-β1 expression. *Hypertension* 2002;**39**:281—6.
56. Gatua WK, Makumi JN, Njagi EM, Kigondu CS, Mcligeyo SO, Waithaka SK. Evaluation of urinary tubular enzymes as screening markers of renal dysfunction in patients suffering from diabetes mellitus. *Asian J Med Sci* 2011;**3**:84—90.
57. De Carvalho JA, Piva SJ, Hausen BS, Bochi GV, Kaefer M, Coelho AC, et al. Assessment of urinaryγ-glutamyltransferase and alkaline phosphatase for diagnosis of diabetic nephropathy. *Clin Chim Acta* 2011;**412**:1407—11.
58. Agarwal R, Vasavada N, Sachs NG, Chase S. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. *Kidney Int* 2004;**65**:2279—89.
59. Temkin V, Karin M. From death receptor to reactive oxygen species and c-Jun N-terminal protein kinase: the receptor-interacting protein 1 odyssey. *Immunol Rev* 2007;**220**:8—21.
60. Verzola D, Bertolotto MB, Villaggio B, Ottonello L, Dallegri F, Salvatore F, et al. Oxidative stress mediates apoptotic changes induced by hyperglycemia in human tubular kidney cells. *J Am Soc Nephrol* 2004;**15**:S85—7.
61. Devuyst O, Konrad M, Jeunemaitre X. Oxidative stress in the kidney: Proximal tubule disorders. In: Miyata T, Eckardt KU, Nangaku M, editors. *Oxidative stress in applied basic research and clinical practice — Studies on renal disorders*. 1st ed. Humana Press and Springer Science; 2011. p. 179—203.
62. Diwakar R, Pearson AL, Colville-Nash P, Brunskill NJ, Dockrell ME. The role played by endocytosis in albumin-induced secretion of TGF-beta1 by proximal tubular epithelial cells. *Am J Physiol Renal Physiol* 2007;**292**:F1464—70.